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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. |
|---|---|---|---|

| EXAMINER | |
|---|---|
| ART UNIT | PAPER NUMBER |

**DATE MAILED:**

**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**

# Office Action Summary

| Application No. | Applicant(s) |
|---|---|
| 989,846 | GEHRMANN et al |
| **Examiner** | **Group Art Unit** |
| SAUNDERS | 1644 |

*—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—*

**Period for Response**

A SHORTENED STATUTORY PERIOD FOR RESPONSE IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a response be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for response specified above is less than thirty (30) days, a response within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for response is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to respond within the set or extended period for response will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

**Status**

- [x] Responsive to communication(s) filed on 10/20/99.
- [ ] This action is **FINAL.**
- [ ] Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle,* 1935 C.D. 1 1; 453 O.G. 213.

**Disposition of Claims**

- [x] Claim(s) 1-33 is/are pending in the application.
  - Of the above claim(s) 14-22 is/are withdrawn from consideration.
- [ ] Claim(s) _____ is/are allowed.
- [x] Claim(s) 1-13, 23-33 is/are rejected.
- [ ] Claim(s) _____ is/are objected to.
- [ ] Claim(s) _____ are subject to restriction or election requirement.

**Application Papers**

- [x] See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
- [ ] The proposed drawing correction, filed on _____ is [ ] approved [ ] disapproved.
- [ ] The drawing(s) filed on _____ is/are objected to by the Examiner.
- [x] The specification is objected to by the Examiner.
- [ ] The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. § 119 (a)-(d)**

- [x] Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).
  - [ ] All [ ] Some* [ ] None of the CERTIFIED copies of the priority documents have been
  - [ ] received.
  - [x] received in Application No. (Series Code/Serial Number) 08/743,372.
  - [ ] received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received: _____.

**Attachment(s)**

- [x] Information Disclosure Statement(s), PTO-1449, Paper No(s). 3
- [x] Notice of References Cited, PTO-892
- [x] Notice of Draftsperson's Patent Drawing Review, PTO-948
- [ ] Interview Summary, PTO-413
- [ ] Notice of Informal Patent Application, PTO-152
- [ ] Other _____

**Office Action Summary**

The claims pending are 1-33.

Applicant's election of Group I (claims 1-13 and 23-26 in Paper No. 5 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Newly submitted claims 27-33 are considered to fall within Group I and are thus under examination.

The disclosure is objected to because of the following informalities: Specification page 1 lacks a section referring to parent applications and the current status of each.

Appropriate correction is required.

Other items in the specification requiring correction include:

The specification fails to comply with 37 CFR 1.58(a) by virtue of containing drawings at pages 10-15. These must be canceled from the specification and submitted on separate drawing sheets. A section headed "Brief Description of the Drawings" must be added to the specification that describes the drawings without entry of new matter. It is also noted that pages 17-24 refer to various Figures that have not been described in a "Brief Description of the Drawings". Furthermore, these Figures require renumbering so that they fit in sequence with those to be earlier referenced at pages 10-15.

At specification pages 25-29 and 33-36 the tables 1-3 should be canceled. These contain material now presented in the SEQ ID NO: listing and are hence wasteful of space. References

to these "Tables" in the specification require deletion and replacement with references to SEQ ID NOS: Tables 4-6 at pages 30-32 require renumbering as 1-3. All specification references to these must be corrected.

Claim 26 is rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific asserted utility or a well established utility.

Claim 26 is drawn to a composition containing the compound of claim 1 as a diagnostic aid. It is noted that the compound recited in claim 1 contains a prodrug-activating enzyme. Since activation of prodrugs to active drugs is not a conventional step of immuno-diagnostic methods, one of skill would not readily envision how to use the recited compound as a diagnostic aid. Applicant has given no direction as to how this compound is to be used--e.g. what analyte is being tested for, what read-out signal is obtained, etc.

Claim 26 is also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claims 1-13 and 23-33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite by reciting "antigen binding region" and then reciting "which is bound", both at line 1. This implies that the antigen binding region binds the enzyme; however

such is not the disclosed invention. Substitution of an equivalent and supportable term in lieu of "bound" would be appropriate.

Claims 3 and 30 are unclear by being inconsistent with base claim 1. These dependent claims are directed to a compound containing SFV, which would be a monovalent, not bivalent or multivalent. Note the exemplified SFV-huB-gluc is encoded by only one each of VH and (a VL encoding gene.

Claims 5 and 6 recite an improper Markush group. Recitation of "essentially" is an improper introduction of the Markush group members.

In claim 5, line 1 "the TAA" lacks antecedent basis in claim 3.

Claim 7 is unclear by reciting "B-glucuronidase". The subgenuses of enzymes recited in its base claim 6 do not apparently encompass a glucuronidase. Thus claim 7 would more appropriately depend directly from 1.

In claims 10 and 13 "undergoes" is unclear. By being in the present tense applicant appears to be reciting, in an improper format, an intended method of use of the compound. Recitation of a past tense "has undergone" as in claim 12, would be appropriate.

In claim 27 --Bacillus-- has been misspelled.

Claims 23-24 provides for the use of the compound of claim 1, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claims 23-24 are is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-9, 23-27,30 and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bosslet et al (Brit. J. Cancer 65, 235, 1992 or Seeman et al (EP 0,501,215, English equivalent is CA 2,062,047) in view of Huston et al and as necessary Bosslet et al (EP 0,040,097, English equivalent is US 5,591,828) and Eaton et al (EP 0,392,745).

The Bosslet et al and Seemann et al primary references have essentially the same disclosure showing a fusion protein comprising an Fab (derived from a humanized version of anti-CEA antibody 431), a linker, and a human B-glucuronidase. This protein differs from that instantly claimed by virtue of having an Fab (composed of H and L claims) instead of having and antigen binding region compound of a single polypeptide (e.g. an sFv) formed from VH and VL segments. Huston et al teach that such antigen binding region may be present in multiple copies (col.4, lines 21-36 and col.9, lines 29-31) and that the antigen binding region(s) may be fused to other functional molecules such as enzymes (col.3, line 66-col.4, line 4, col.8, lines 4-6) and col.9 lines 17-28). When the fusion polypeptide is expressed in a eukaryotic host (Huston et al at col.11, lines 19-20 and col.16, lines 1-7) one would have expected the polypeptide to be glycosylated in accord with instant claims 2 and 9.

The essence of the obviousness rejection is that it would have been obvious to modify the fusion protein constructs of the primary reference by substituting the single chain antigen binding polypeptides of Huston et al for the Fab of the construct. Motivations to make this substitution are as follows:

1) Huston et al teach enzymes can be fused to the antigen binding region(s). One would have hence fully expected the glucuronidase enzyme taught by Bosslet et al or Seeman et al to be useable when fused to the single chain constructs of Huston et al.

2) One of ordinary skill in the art would have recognized Fab, Fv and the chain constructs of Huston et al as functional equivalents in terms of antigen binding. See Huston et al at col.3,

lines 42-52; col.19, lines 9-30. Note also that Eaton et al teaches Fv fragments may be used as the antigen binding entity in conjugates containing prodrug activating enzymes.

3) One would have been motivated to use the sFv of Huston et al in lieu of Fab since the former can have increased stability, and can penetrate tissues more rapidly than antibodies or their conventionally produced fragments. See col.4, lines 10-20.

4) One would have been motivated to provide the constructs of Huston et al with two or more antigen binding regions because such would increase the overall affinity/avidity of the protein when binding to cell surfaces that present multiple copies of the antigen. See Huston et al at col.4, lines 21-37. See Bosslet et al ('097) at Fig.3 and discussion associated therewith for a teaching of how a polypeptide can be provided with two oppositely oriented antigen binding regions within a single polypeptide.

5) Form the above considerations set forth in parts 3) and 4) one would have expected that, due to the lower size of sFv compared to Fab, one would have been able to provide a construct that has at least bivalency for antigen (as opposed to monovalency when one provided an Fab) without significantly increasing the size of the construct over that containing an Fab. One would have thus gained the above noted advantage of increased affinity/avidity without significant loss of tissue penetrating capacity of the polypeptide.

6) One would have expected an inherent advantage to be gained by using the single chain constructs of Huston et al in that one would only need to transfect cells with one instead of two

vectors in order to obtain expression of the protein. Compare Huston et al at col.18, lines 5-31 with Bosslet et al at page 235, col.1, last paragraph.

As to the limitations set forth in dependent claims that have not been implicitly or explicitly addressed supra note the following.

Claims 23-25 and 33 are directed to a pharmaceutical composition, use thereof, and method of treatment. The Bosslet et al disclosure teaches potential therapeutic use (page 238). Seemann et al likewise teach use of the fusion proteins in humans (page 1). The above noted portions of Huston et al teachings improved tissue penetration clearly have a body treatment in consideration.. Thus claims 23-25 and 33 would have been obvious.

Claims 23 and 26 are drawn to a diagnostic composition or use thereof. Each claim recites merely an intended use that carries no weight and does not distinguish the polypeptide from what it would be in any composition in which it would bind to antigen and have enzymatic activity. Clearly such compositions would include those wherein the binding and enzymatic activity of the polypeptide is evaluated --e.g. Bosslet et al at pages 235-236, Huston et al at col.19.

Claims 27 and 30 require that the prodrug activating enzyme be a beta-lactamase, which is taught by Eaton et al as a prodrug-activating enzyme. They furthermore point one to use of this enzyme obtained from B. Cereus (page 4, line 14).

Claims 1,11-12 and 31-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bosslet et al or Seemann et al in view of Huston et al and as necessary Bosslet et al and Eaton et

al as applied to claim s 1-9,23-27,30 and 33 above, and further in view of Ong et al (Cancer Res. 51, 619,1991), Bagshawe et al (WO89/10140), and Huston et al (Methods Enzmol., 204,46,1991).

The above stated rejection of claim 1 was based upon teachings of the production of a fusion polypeptide without particular consideration of the host cell to be employed for its expression. Only in the case of claims 2 and 9 did the examiner point to the use of eukaryotic cells, which would have been expected to provide glycosylation.

Huston et al (methods...page 70) teach that polypeptides containing sFv may be secreted into the periplasmic space of Gram-negative bacteria and be properly refolded with the correct disulfide bonds. Since E.Coli are more easily grown than many eukaryotic cells, such as myeloma cells, one would have been motivated to use an E. Coli expression system capable of providing correctly folded proteins in large amounts. One of ordinary skill would have recognized that polypeptides produced by E.Coli would not be glycosylated.

Ong et al teach that it is advantageous to permit rapid clearing of circulating therapeutic antibodies in a treated individual by providing galactosyl moieties on the antibodies. These authors particularly teach that such clearing would be advantageous in cases wherein antibody-enzyme conjugates that convert a prodrug to an active drug are employed. Since, as noted supra in the rejection of claim 1, antibody enzyme conjugates and sFv-enzyme fusion proteins are functionally equivalent it would have been obvious to provide galactosyl moieties on sFv-enzyme fusion proteins, so that these could be rapidly cleared from the circulation. One of

ordinary skill would have known that when a polypeptide is expressed in a prokaryote, such as E-Coli (taught by Huston et al methods..., at page 70) there is no glycosylation, and, hence, such expressed polypeptide could be subsequently glycosylated with galactose moieties according to a chemical method, such as that taught by Ong et al (page 1620), col.1).

Bagshawe et al will also be relied upon for teaching the desirability of placing galactosyl and/or mannosyl moieties on an antibody that is a member of an antibody-prodrug activating enzyme conjugate. See page 9, lines 1-5 and page 10, lines 6-25. The blocking and clearing strategy taught therein is akin to that taught by Ong et al at pages 1622-1624. From the teachings of Ong et al and Bagshawe et al, either together or each alone, one would have had ample motivation to provide galactosyl or other carbohydrates residues taught by Bagshawe et al (page 13) on sFv-enzyme fusion proteins.

Claims 10,13 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bosslet et al or Seemann et al in view of Huston et al and as necessary Bosslet et al and Eaton et al and further in view of Ong et al, Bagshawe et al and Huston et al as applied to claims 1,11-12 and 32-33 above, and further in view of Goochee et al (Biotechnol, 9, 1347, 1991).

The above rejections have noted that one would have realized that it would have been desirable to provide a galactosylated or mannosylated polypeptide in order to enhance clearance of unbound peptide from the circulation.

Goochee et al at page 7 show that it was known that yeast could be used to express polypeptide having a high degree of mannosylation and having a rapid clearance rate. It hence

would have been obvious to express the polypeptide of claim 1 in such yeast in order to provide polypeptide having mannose moieties that would allow for effective clearance of the polypeptide.

The species recited in claim 13 is specifically taught by Goochee et al at page 1348 The species recited in claim 29 is not specifically taught at page 1348; however, Goochee et al teach most yeast strains provide such mannose moieties and it would have been within the ordinary skill of one in the art to determine which yeast species and strains would be appropriate.

Claims 1 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bosslet et al or Seemann et al in view of Huston et al and as necessary Bosslet et al and Eaton et al as applied to claims 1-9,23-27, 30 and 33 above, and further in view of Bagshawe et al (WO 88/07378).

Bagshawe et al show the further feature that it was known and conventional to provide carboxypeptidase G2 from pseudomonas as a prodrug activating enzyme in antibody enzyme conjugates for therapy.

Claims 1-10,12-13,25-26,30 and 33 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-10,12-13,25-26 and 28-29 of copending Application No. 09/178,564. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

The above rejected claims are verbatim duplicates of the copending claims.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321© may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 11,23-24,27-29 and 31-32 provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 6,10-11 and 30 of copending Application No. 09/178,564. Although the conflicting claims are not identical, they are not patentably distinct from each other because while the pending and copending claims are not verbatim duplicates, they differ in only minor ways e.g. as to their scope. Nevertheless the instant and copending claims clearly claim at common subject matter. Hence issuing the instant claims without a disclaimer would improperly extend patent rights.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

No copy of Pat 5,591,828 has been provided with this Office action. A copy of this reference was provided to applicant during examination of copending application 09/178,564.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David A. Saunders, Ph.D whose telephone number is (703) 308-2976. The examiner can normally be reached on M-F from 8:15 to 4:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan, can be reached on (703) 308-3973. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

David A. Saunders

DAVID SAUNDERS
PRIMARY EXAMINER
ART UNIT ~~182~~ 1644

Saunders/sg

January 11, 2000